Obesity ups cancer risk, and here's how

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Obesity comes with plenty of health risks, but there's one that's perhaps not so well known: an increased risk of developing cancer, and especially certain types of cancer like liver cancer. Now, a group of researchers reporting in the January 22nd issue of the journal *Cell*, a Cell Press publication, have confirmed in mice that obesity does indeed act as a "bona fide tumor promoter." They also have good evidence to explain how that happens.

"Doctors always worry about our weight, but the focus is often on cardiovascular disease and type 2 diabetes, both of which can be managed pretty well with existing drugs," said Michael Karin of the University of California, San Diego. "However, we should also worry about elevated cancer risk. If we can reduce cancer deaths by as many as 90,000 per year, that's a lot of people - a lot of lives."

Karin's team shows that liver cancer is fostered by the chronic inflammatory state that goes with obesity, and two well known inflammatory factors in particular. The findings suggest that anti-inflammatory drugs that have already been taken by millions of people for diseases including rheumatoid arthritis and Crohn's disease may also reduce the risk of cancer in those at high risk due to obesity and perhaps other factors as well, Karin said.

The epidemiological studies reported earlier showed that obese people have about a 1.5-fold increase in their risk of cancer overall. That may not necessarily sound like a lot, Karin said, but it equates to about 90,000 extra cancer deaths per year in the United States alone. When it comes to

liver cancer, the study showed obese people have a 4.5-fold greater risk.

Given the apparent connection between obesity and liver cancer in particular, Karin's team decided to investigate in mice prone to develop hepatocellular carcinoma (HCC). The mice are typically given HCC either by exposure to a chemical carcinogen, known as DEN, when they are two weeks old, or by exposure to that same carcinogen at three months of age followed by the tumor-promoting chemical phenobarbitol.

In the new study, the researchers gave two-week-old mice DEN and then divided them into two groups - one fed a normal, relatively low-fat food and the other fed on high-fat chow. "It was clear that the mice on the high fat diet developed more liver cancer," Karin said.

To further confirm the link, they gave DEN to two-week-old mice that were fed a normal diet but carried a gene that made them obesity-prone. Those mice, too, developed more liver cancers, evidence that it wasn't the high-fat diet that led to cancer, but rather something about the animals obese state.

But Karin said perhaps the biggest surprise came in studies of mice on a high-fat diet who were given DEN a little later in life, when they were three-months-old. Normally, mice on the standard diet given the chemical at that age really don't develop liver cancer unless DEN exposure is followed up with phenobarbitol, Karin explained. But the obese mice developed the disease without that extra push.

"We expected to see more cancer in our first experiments, but I was stunned to see here that only the mice who were obese developed the cancer," Karin said. "Obesity appears to be as strong as phenobarbitol; we can conclude, at least in mice, that obesity is a real tumor promoter."

His team was able to trace the source of obesity's tumor-promoting

effect to a rise in two inflammatory factors known as IL-6 and TNF. Obese mice lacking either the TNF receptor or IL-6 don't show the same rise in liver cancer.

Those treatments also led the mice to accumulate less fat in their livers, he said. "They still get fat, but the distribution of the fat is different," he said. "The fat goes to other places, but not to the liver."

Karin suggests that clinical studies of people who are already taking anti-TNF drugs should be done, to find out if their livers are less fatty and cancer-free.

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